REMARKS

Applicants respectfully submit that the foregoing amendments merely correct clerical errors, are adequately supported by the specification as originally filed and do not raise any issues of new matter. The amendments correct errors in sequence coordinates identifying portions of SEQ ID NOs: 7 and 8 that correspond to the PDGF-D proteins, fragments or functional domains. The information contained entirely within the specification supports these amendments. Specifically,

(1) with regard to SEQ ID NO: 7, the specification and claims previously indicate that its coding sequence was from positions 173-1288, but an examination of SEQ ID NO: 7 clearly indicates that the correct positions should be 176-1285 (paragraph 35 and claims 1 and 4);

(2) also with regard to SEQ ID NO: 7, the reference to 938-1288 has been corrected to be 935-1285 (position 935 is where the RKSK site starts) (paragraphs 35 and claims 1 and 4);

(3) with regard to SEQ ID NO: 8, the RKSK site was incorrectly identified as residues 255-258. This plain error is now corrected to read 254-257 (paragraph 0079). Also, the length of SEQ ID NO: 8 is corrected to be 370 to match the actually sequence (paragraph 092);

(4) the CUB domain was identified as residues 54-171 of SEQ ID NO: 8 in paragraph 123, yet it should be 53-170 according to the sequence shown in Figure 12 (CUB domain sequence for hPDGF-D should be DETT...); and

(5) finally there is a typographical error in paragraph 128, where a 19 amino acid fragment corresponding to residues 254-272 of SEQ ID NO: 36 was

mistakenly recited to contain an extra C (making it 20 amino acid long), and identified as SEQ ID NO: 35. Both mistakes have now been corrected.

Because the above amendments merely correct clerical errors and do not add new matter, entry of the amendments to the specification and claims before examination of the application is respectfully requested.

If there are any questions regarding this Preliminary Amendment or this application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

Respectfully submitted,

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VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE SPECIFICATION:

Paragraph [0035] has been amended as follows:

[0035] According to one aspect, the invention provides an isolated nucleic acid molecule which comprises a polynucleotide sequence having at least 85% identity, more preferably at least 90%, and still more preferably at least 95% identity, and most preferably at 100% identity to at least nucleotides 1 to 600 of the sequence set out SEQ ID NO:3, at least nucleotides 1 to 966 of the sequence set out in SEQ ID NO:5, at least nucleotides [173 to 1288] 176 to 1285 of the sequence set out in SEQ ID NO:7 at least nucleotides [938 to 1288] 935 to 1285 set out in SEQ ID NO:7, at least nucleotides 1 to 1110 of SEQ ID NO:35, at least nucleotides 1-1092 of SEQ ID NO:37, or SEQ ID NO:39. The sequence of at least nucleotides 1 to 600 of the sequence set out in Figure 3 (SEQ ID NO:3) or at least nucleotides 1 to 966 of the sequence set out in Figure 5 (SEQ ID NO:5) encodes a 5'-truncated polypeptide, designated PDGF-D (formally designated "VEGF-G"), while at least nucleotides [to 1288] 176 to 1285 of the sequence set out in Figure 7 (SEQ ID NO:7) encodes a full-length PDGF-D. The sequence of at least nucleotides 1 to 1110 of SEQ ID NO:35 encodes a murine PDGF-D, while the sequence of at least nucleotides 1-1092 of SEQ ID NO:37 encodes an identical protein as SEQ ID NO:35 except for a six amino acid residue gap (a.a. #42-47) from the region between the signal sequence and the CUB domain (see below for details) , and SEQ ID NO:39 a C-terminal truncated protein of the polypeptide encoded by SEQ ID NO:35. The PDGF-D polynucleotide of the invention can be a naked plynucleotide and/or in a vector or liposome.

Paragraph [0036] has been amended as follows:

[0036] PDGF-D is structurally homologous to PDGF-A, PDGF-B, VEGF, VEGF-B, VEGF-C and VEGF-D. The sequence of at least nucleotides [938 to 1288] 935 to 1285 set out in Figure 7 (SEQ ID NO:7) encodes a portion of the PDGF/VEGF homology domain, which is the bioactive fragment of PDGF-D.

This bioactive fragment would also be encoded by the sequence of at least nucleotides 1 to 600 of the sequence set out in Figure 3 (SEQ ID NO:3) or at least nucleotides 1 to 966 of the sequence set out in Figure 5 (SEQ ID NO:5).

Paragraph [0038] has been amended as follows:

[0038] A preferred fragment is a truncated form of PDGF-D comprising a portion of the PDGF/VEGF homology domain (PVHD) of PDGF-D. The portion of the PVHD is from residues [255-371] 254-370 of Figure 8 (SEQ ID NO:8) where the putative proteolytic processing site RKSK starts at amino acid residue [255] 254 (SEQ ID NO:8). However, the PVHD extends toward the N terminus up to residue [235] 234 of Figure 8 (SEQ ID NO:8). Herein the PVHD is defined as truncated PDGF-D. The truncated PDGF-D is the putative activated form of PDGF-D.

Paragraph [0079] has been amended as follows:

[0079] Another aspect of the invention relates to the discovery that the full length PDGF-D protein is likely to be a latent growth factor that needs to be activated by proteolytic processing to release an active PDGF/VEGF homology domain. A putative proteolytic site is found in residues [255-258] 254-257 in the full length protein, residues -RKSK- (SEQ ID NO:9). This is a dibasic motif. The -RKSK- (SEQ ID NO:9) putative proteolytic site is also found in PDGF-A, PDGF-B, VEGF-C and VEGF-D. In these four proteins, the putative proteolytic site is also found just before the minimal domain for the PDGF/VEGF homology domain. Together these facts indicate that this is the proteolytic site.

Paragraph [0092] has been amended as follows:

[0092] Figure 7 (SEQ ID NO:7) shows the complete nucleotide sequence of cDNA encoding a hPDGF-D(1116 bp) and the deduced amino acid sequence of full-length hPDGF-D encoded thereby which consists of [371] 370 amino acid residues (Figure 8-SEQ ID NO:8);

Paragraph [00123] has been amended as follows:

[00123] The N-terminal region of the partial PDGF-D amino acid sequence of Figure 12 (residues 53-170 [54-171] of SEQ ID NO:8) has a second distinct protein domain which is referred to as a CUB domain (Bork and Beckmann, J. Mol. Biol., 1993 231, 539-545). This domain of about 115 amino acids was originally identified in complement factors C1r/C1s, but has recently been identified in several other extracellular proteins including signaling molecules such as bone morphogenic protein 1 (BMP-1) (Wozney *et al.*, Science, 1988 242, 1528-1534) as well as in several receptor molecules such as neuropilin-1 (NP-1) (Soker *et al.*, Cell, 1998 92 735-745). The functional roles of CUB domains are not clear but they may participate in protein-protein interactions or in interactions with carbohydrates including heparin sulfate proteoglycans. These interactions may play a role in the proteolytic activation of PDGF-D.

Paragraph [00128] has been amended as follows:

[00128] Rabbit antisera against full-length PDGF-DD and against a synthetic peptide derived from the PDGF-D sequence (residues 254-272, amino acid sequence [CRKSKVDLDRLNDDAKRYSC] RKSKVDLDRLNDDAKRYSC of SEQ ID NO:36) [(SEQ ID NO:35))] were generated. These peptides were each conjugated to the carrier protein keyhole limpet hemocyanin (KLH, Calbiochem) using N-succinimidyl 3-(2-pyridyldithio)propionate (SPDP) (Pharmacia Inc.) according to the instructions of the supplier. 200-300 micrograms of the conjugates in phosphate buffered saline (PBS) were separately emulsified in Freunds Complete Adjuvant and injected subcutaneously at multiple sites in rabbits. The rabbits were boostered subcutaneously at biweekly intervals with the same amount of the conjugates emulsified in Freunds Incomplete Adjuvant. Blood was drawn and collected from the rabbits. The sera were prepared using standard procedures known to those skilled in the art. The antibodies to full-length PDGF-DD were affinity-purified on a column of purified PDGF-DD coupled to CNBr-activated Sepharose 4B (Pharmacia).

IN THE CLAIMS:

Claims 1, 4 and 16 has been amended as follows:

1. (Amended) An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having a PDGF-D activity and having a sequence identity of at least 85% with at least nucleotides 1 to 600 of SEQ ID NO:3, at least nucleotides 1 to 966 of SEQ ID NO:5, at least nucleotides [176-1288] 176-1285 SEQ ID NO:7, at least nucleotides [938 to 1288] 935 to 1285 of SEQ ID NO:7, at least nuleotides 1-1110 of SEQ ID NO:35, or at least nucleotides 1-1092 of SEQ ID NO:37, or a polynucleotide which hybridizes under stringent conditions with at least one of said sequences.

4. (Amended) An isolated nucleic acid molecule according to Claim 1, wherein the nucleic acid molecule comprises a polynucleotide having at least nucleotides 1 to 600 of SEQ ID NO:3, at least nucleotides 1 to 966 of SEQ ID NO:5, at least nucleotides [176-1288] 176-1285 SEQ ID NO:7, at least nucleotides [938 to 1288] 935 to 1285 of SEQ ID NO:7, at least nuleotides 1-1110 of SEQ ID NO:35, or at least nucleotides 1-1092 of SEQ ID NO:37.

16. (Amended) An isolated polypeptide having a biological activity of PDGF-D and comprising an amino acid sequence having at least 85% identity with SEQ ID NOs:4, 6, 8, 36, 38, or at least the amino acid residues [255 to 371] 254 to 370 of SEQ ID NO:8, or a fragment or analog thereof having the biological activity of PDGF-D.